PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 September 2000 (08.09.00)	
International application No. PCT/US99/19307	**Applicant's or agent's file reference** 110209-ASH
International filing date (day/month/year) 25 August 1999 (25.08.99)	**Priority date** (day/month/year) 25 August 1998 (25.08.98)
Applicant ASH, Stephen, R.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 March 2000 (24.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Manu Berrod
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

ASH MEDICAL SYSTEMS, INC., etal. | 110209-ASH

ENTITLED
METHOD OF ENHANCING [redacted]TER PATENCY USING A CITRAT[redacted] CATHETER LOCK SOLUTION

Certification under 37 CFR 1.10 (if applicable)

EL016470850US — "Express Mail" mailing number

25 August 1999 — Date of Deposit

I hereby certify that this application is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

LINDA C. SHELBY — (Typed or printed name of person mailing application)

Linda C. Shelby — (Signature of person mailing application)

To the United States Receiving Office (RO/US):

Accompanying this transmittal letter is the above-identified International application, including a completed Request form (PCT/RO/101). Please process the application according to the provisions of the Patent Cooperation Treaty.

The following requests are made of the RO/US:

1. [XX] PREPARATION AND TRANSMITTAL OF CERTIFIED COPY OF PRIORITY DOCUMENTS—Please prepare and transmit to the International Bureau a certified copy of the United States origin priority documents identified in Box VI of the Request form (37 CFR 1.451).

   To cover the cost of copy preparation and certification (37 CFR 1.19(a)(2) and (b)(1)),
   [XX] a (check) (money order) in the amount of $15.00 included in Fee is attached to this transmittal letter.
   [ ] the RO/US is hereby authorized to charge the following deposit account no.: _____.

2. [XX] CHOICE OF INTERNATIONAL SEARCHING AUTHORITY—It is requested that the International Search be performed by the following International Searching Authority:

   [XX] United States Patent and Trademark Office (ISA/US)

   [ ] European Patent Office (ISA/EP)

   The appropriate Search fee for the above-named Authority is indicated on the Fee Calculation Sheet (PCT/RO/101 Annex).

3. [XX] SUPPLEMENTAL SEARCH FEES (ONLY WHEN ISA/US CONDUCTS THE INTERNATIONAL SEARCH.)—Please charge any Supplemental Search fees that may be required by the United States International Searching Authority (ISA/US) to deposit account no.: 23-3030.

   I understand that this authorization is subject to my oral confirmation thereof in each instance and that it in no way limits my right to submit a protest against payment of the Supplemental Search fees, but is merely an administrative aid to assure that the ISA/US may timely complete the Search Report.

NOTE: SUPPLEMENTAL SEARCH FEES FOR ISA/EP ARE PAYABLE DIRECTLY TO THE EUROPEAN PATENT OFFICE

4. [XX] DISCLOSURE INFORMATION—In order to assist in screening the accompanying International application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied:

   A. [ ] There is no prior filed application relating to this invention.

   B. [XX] There is a prior application, serial number 60/097,777 filed on 25 August 1998 (25.08.9 which contains subject matter that is

      1. [XX] substantially identical to that of the accompanying International application.
      2. [ ] less than that of the accompanying International application. The additional subject matter of the International application appears on pages(s) and line(s) _____.
      3. [ ] more than that of the accompanying International application.

   C. [ ] Disclosure information cannot be covered by the language of Points 4A or 4B above due to the involvement of several prior applications or for other reasons. A separate sheet on which the disclosure information is explained is attached to this transmittal letter.

5. [XX] REQUEST FOR FOREIGN TRANSMITTAL LICENSE—According to the provisions of 35 U.S.C. 184 and 37 CFR 5.11, a license to transmit the accompanying International application to foreign agencies or international authorities is hereby requested.

SIGNER IS THE	NAME OF SIGNER (typed)
[ ] APPLICANT [ ] COMMON REPRESENTATIVE [X] (ATTORNEY) (AGENT) REG NO 40,967	Gregory B. COY SIGNATURE

PTO-1382 (REV 3-84)
USCOMM DC 84 3817

U.S. Department of Commerce
Patent and Trademark Office

PCT

FEE CALCULATION SHEET
Annex to the Request

receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 110209-ASH

Applicant: ASH MEDICAL SYSTEMS, INC., etal.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 240 [T]

2. SEARCH FEE . . . . . 700 [S]

International search to be carried out by US

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 43 sheets.

first 30 sheets . . . . . 455 [b1]

13 remaining sheets x 10 additional amount = 130 [b2]

Add amounts entered at b1 and b2 and enter total at B . . . . 585 [B]

Designation Fees

The international application contains 80 designations.

10 number of designation fees payable *(maximum 10)* x 105 amount of designation fee = max. 1050 [D]

Add amounts entered at B and D and enter total at I . . . . . 1635 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 15 [P]

5. TOTAL FEES PAYABLE . . . . . 2590 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

[XX] authorization to charge deposit account (see below)	[ ] bank draft	[ ] coupons
[XX] cheque	[ ] cash	[ ] other *(specify):*
[ ] postal money order	[ ] revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ US [ ] is hereby authorized to charge the total fees indicated above to my deposit account.

[XX] *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

[ ] is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

23-3030 — Deposit Account No.

25/August/1999 — Date *(day/month/year)*

Signature Gregory B. COY, 40,967

Form PCT/RO/101 (Annex) (January 1999)

See Notes to the fee calculation sheet

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Appli[redacted] No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 110209-ASH

Box No. I TITLE OF INVENTION METHOD OF ENHANCING CATHETER PATENCY USING A CITRATE SALT CATHETER LOCK SOLUTION

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASH MEDICAL SYSTEMS, INC.
2701-B Kent Avenue
West Lafayette, Indiana 47906 US

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASH, Stephen R.
3736 Pershing Drive
Lafayette, Indiana 47905 US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

COY, Gregory B.
WOODARD, EMHARDT, NAUGHTON, MORIARTY & MCNETT
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, Indiana 46204 US

SEE CONTINUATION TO BOX NO. IV ON SHEET NO. 3

Telephone No. 317-634-3456

Facsimile No. 317-637-7561

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH** and **LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] **AE** United Arab Emirates
- [X] **AL** Albania .....
- [X] **AM** Armenia .....
- [X] **AT** Austria .....
- [X] **AU** Australia .....
- [X] **AZ** Azerbaijan
- [X] **BA** Bosnia and Herzegovina .....
- [X] **BB** Barbados
- [X] **BG** Bulgaria .....
- [X] **BR** Brazil .....
- [X] **BY** Belarus .....
- [X] **CA** Canada
- [X] **CH and LI** Switzerland and Liechtenstein
- [X] **CN** China .....
- [X] **CU** Cuba .....
- [X] **CZ** Czech Republic .....
- [X] **DE** Germany .....
- [X] **DK** Denmark .....
- [X] **EE** Estonia .....
- [X] **ES** Spain .....
- [X] **FI** Finland .....
- [X] **GB** United Kingdom
- [X] **GD** Grenada
- [X] **GE** Georgia .....
- [X] **GH** Ghana .....
- [X] **GM** Gambia
- [X] **HR** Croatia .....
- [X] **HU** Hungary .....
- [X] **ID** Indonesia
- [X] **IL** Israel .....
- [X] **IN** India .....
- [X] **IS** Iceland
- [X] **JP** Japan .....
- [X] **KE** Kenya .....
- [X] **KG** Kyrgyzstan .....
- [X] **KP** Democratic People's Republic of Korea .....
- [X] **KR** Republic of Korea .....
- [X] **KZ** Kazakhstan .....
- [X] **LC** Saint Lucia
- [X] **LK** Sri Lanka
- [X] **LR** Liberia
- [X] **LS** Lesotho .....
- [X] **LT** Lithuania
- [X] **LU** Luxembourg
- [X] **LV** Latvia
- [X] **MD** Republic of Moldova .....
- [X] **MG** Madagascar .....
- [X] **MK** The former Yugoslav Republic of Macedonia .....
- [X] **MN** Mongolia
- [X] **MW** Malawi .....
- [X] **MX** Mexico .....
- [X] **NO** Norway
- [X] **NZ** New Zealand .....
- [X] **PL** Poland .....
- [X] **PT** Portugal .....
- [X] **RO** Romania
- [X] **RU** Russian Federation .....
- [X] **SD** Sudan
- [X] **SE** Sweden
- [X] **SG** Singapore
- [X] **SI** Slovenia .....
- [X] **SK** Slovakia .....
- [X] **SL** Sierra Leone .....
- [X] **TJ** Tajikistan .....
- [X] **TM** Turkmenistan .....
- [X] **TR** Turkey .....
- [X] **TT** Trinidad and Tobago .....
- [X] **UA** Ukraine .....
- [X] **UG** Uganda .....
- [X] **US** United States of America .....
- [X] **UZ** Uzbekistan .....
- [X] **VN** Viet Nam .....
- [X] **YU** Yugoslavia .....
- [X] **ZA** South Africa .....
- [X] **ZW** Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- [X] CR-Costa Rica .....
- [ ] .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;

(vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation to Box No. IV Agent

WOODARD, Harold R.; EMHARDT, C. David; NAUGHTON, Joseph A., Jr.; MORIARTY, John V.; McNETT, John C.; HENRY, Thomas Q.; DURLACHER, James M.; REEVES, Charles R.; WAGNER, Vincent O.; ZLATOS, Steve; BEREVESKOS, Spiro; BAHRET, William F.; BROWNING, Clifford W.; FRISK, R. Randall; LUEDERS, Daniel J.; GANDY, Kenneth A.; THOMAS, Timothy N.; SISSELMAN, Kerry P.; JONES, Kurt N.; ALLIE, John H.; BANTA, Holiday W.; COLE, Troy J.; PAYNTER, L. Scott; LOWES, J. Andrew; MEYER, Charles J.; HARRIS, Darrin Wesley; SCHANTZ, Matthew R.; COY, Gregory B.; HIDAY, Lisa A.; DANILUCK, John V.; BROWN, Christopher A.;SCHWARTZ, Jason J.; USHER, Arthur J. IV; COLLIER, Douglas A.; MYERS, James B. Jr.; STEVENS, Scott J., and ROWE, James L., all of Woodard, Emhardt, Naughton, Moriarty & McNett, Bank One Center/Tower, Suite 3700, 111 Monument Circle, Indianapolis, Indiana 46204 United States of America

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* Regional Office	international application: receiving Office
item (1) (25.08.98) 25 August 1998	60/097,777	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* : ISA / US

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date (day/month/year)	Number	Country (or regional Office)
25 August 1998 (25.08.98)	60/097,777	US

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	4
description (excluding sequence listing part)	:	27
claims	:	7
abstract	:	1
drawings	:	4
sequence listing part of description	:	-
Total number of sheets	:	43

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Transmittal Letter (dup)

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Applicant(s):

ASH MEDICAL SYSTEMS, INC.
ASH, Stephen R.

Agent:

(Gregory B. COY)

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

OCT 20 1999

PCT

From the INTERNATIONAL BUREAU

To:

COY, Gregory, B.
Woodard, Emhardt, Naughton,
Moriarty & McNett
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, IN 46204
ÉTATS-UNIS D'AMÉRIQUE

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 19 October 1999 (19.10.99)	
Applicant's or agent's file reference 110209-ASH	**IMPORTANT NOTIFICATION**
International application No. PCT/US99/19307	International filing date (day/month/year) 25 August 1999 (25.08.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 25 August 1998 (25.08.98)
Applicant ASH MEDICAL SYSTEMS, INC. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
25 Augu 1998 (25.08.98)	60/097,777	US	12 Octo 1999 (12.10.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Taïeb Akremi

Telephone No. (41-22) 338.83.38

WO 00/10385
PCT/US99/19307

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
COY, Gregory, B.
Woodard, Emhardt, Naughton,
Moriarty & McNett
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, IN 46204
ÉTATS-UNIS D'AMÉRIQUE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 02 March 2000 (02.03.00)	
Applicant's or agent's file reference 110209-ASH	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US99/19307	25 August 1999 (25.08.99)	25 August 1998 (25.08.98)

Applicant
ASH MEDICAL SYSTEMS, INC. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,
   HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,
   RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   02 March 2000 (02.03.00) under No. WO 00/10385

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra
Telephone No. (41-22) 338.83.38

RECEIVED

AUG 0 7 2000

Woodard, Emhardt, Naughton, Moriarty & McNett

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
GREGORY B. COY
WOODARD, EMHARDT, NAUGHTON, MORIARTY
&
MCNETT, BANK ONE CENTER/TOWER
111 MONUMENT CIRCLE, SUITE 3700
INDIANAPOLIS, IN 46204

PCT

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year,* 02 AUG 2000

Applicant's or agent's file reference
110209-ASH

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/19307	25 AUG 99	25 AUG 98

Applicant
ASH MEDICAL SYSTEMS, INC.

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

   24 March 2000 (24.03.00)

2. That date of receipt is:

   - [x] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
   - [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
   - [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

   [ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on:

   _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorized officer	Jerry M. Johnson-Vessels Supervisory Paralegal Specialist
Assistant Commissioner for Patent Box PCT Washington, D.C. 20231 Attn:RO/US Facsimile No. 703-305-3230	Telephone No.	Team 1 PCT Operations - IAPD (703) 305-3624 (703) 305-3230 (FAX)

Form PCT/IPEA/402 (July 1998)

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

COY, Gregory, B.
Woodard, Emhardt, Naughton,
Moriarty & McNett
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, IN 46204
ETATS-UNIS D'AMERIQUE

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year) 08 September 2000 (08.09.00)	
Applicant's or agent's file reference 110209-ASH	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US99/19307	25 August 1999 (25.08.99)	25 August 1998 (25.08.98)

Applicant
ASH MEDICAL SYSTEMS, INC. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BY,CH,CR,CU,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,
   HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,
   TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Manu Berrod

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

RECEIVED

DEC 29 2000

Woodard, Emhardt, Naughton, Moriarty & McNett

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: GREGORY B. COY
WOODARD, EMHARDT, NAUGHTON, MORIARTY & MCNETT
111 MONUMENT CIRCLE
BANK ONE CENTER/TOWER, SUITE 3700
INDIANAPOLIS, INDIANA 46204

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	22 DEC 2000
Applicant's or agent's file reference: 110209-ASH	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/19307	25 AUGUST 1999	25 AUGUST 1998

Applicant: ASH MEDICAL SYSTEMS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	SHARON KENNEDY
Facsimile No. (703) 305-3230	Telephone No. (703) 305-0154

Form PCT/IPEA/416 (July 1992)★

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 110209-ASH	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/19307	International filing date *(day/month/year)* 25 AUGUST 1999	Priority date *(day/month/year)* 25 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61M/31/00; and US Cl.: 604/523		
Applicant ASH MEDICAL SYSTEMS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☑ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24 MARCH 2000	11 DECEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON KENNEDY Telephone No. (703) 305-0154

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/19307

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages (See Attached), as originally filed
pages _____, as amended (together with any statement) under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/19307

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-43	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-43	YES
	Claims	None	NO
Industrial Applicability (IA)	Claims	1-43	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-43 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the device and/or the lock solution as claimed. Claims 30-34 and 36 are recently allowed because the prior art does not teach the claimed pH. It is known that a blood pH below 6.8 will cause death, thus, it is unlikely that Antwiler would infuse a solution having a pH lower than 6.5 into the blood steam. Claim 35 is recently allowed because Antwiler does not disclose or suggest the viscosifying agent.

---------- NEW CITATIONS ----------

US 5,665,061 A (ANTWILER) 09 September 1997, Abstract, and col. 3 lines 46-59.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-27, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) 28-32, 34, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Page 33, filed with the letter of 13 November 2000.

This report has been drawn on the basis of the drawings,
page(s) 1-4, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

30. A device comprising:

an intravascular catheter having at least one lumen; and

a pharmaceutically acceptable lock solution positioned within the lumen, said lock solution comprising a citrate salt, wherein said lock solution has a pH level below about 6.5.

31. The device of claim 30 wherein said citrate salt comprises a sodium citrate salt.

32. The device of claim 30 or 31 wherein the lock solution has a pH level between about 4.5 and about 6.5.

33. The device of any of claims 30-32 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

34. The device of any of claims 30-33 wherein the lock solution has a density between about 1.0 and about 1.5 and a viscosity between about 1.5 cP and about 4.0 cP.

35. A kit for accessing a patient's intravascular system, comprising:

a catheter defining therethrough at least one lumen;

a container; and

a catheter lock solution contained within the container, the solution comprising a citrate salt solution and a viscosifying agent dissolved or dispersed in the solution.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A01M 59/00, A61M 5/32

A1

(11) International Publication Number: WO 00/10385

(43) International Publication Date: 2 March 2000 (02.03.00)

(21) International Application Number: PCT/US99/19307

(22) International Filing Date: 25 August 1999 (25.08.99)

(30) Priority Data:
60/097,777 25 August 1998 (25.08.98) US

(71) Applicant *(for all designated States except US)*: ASH MEDICAL SYSTEMS, INC. [US/US]; 2701-B Kent Avenue, West Lafayette, IN 47906 (US).

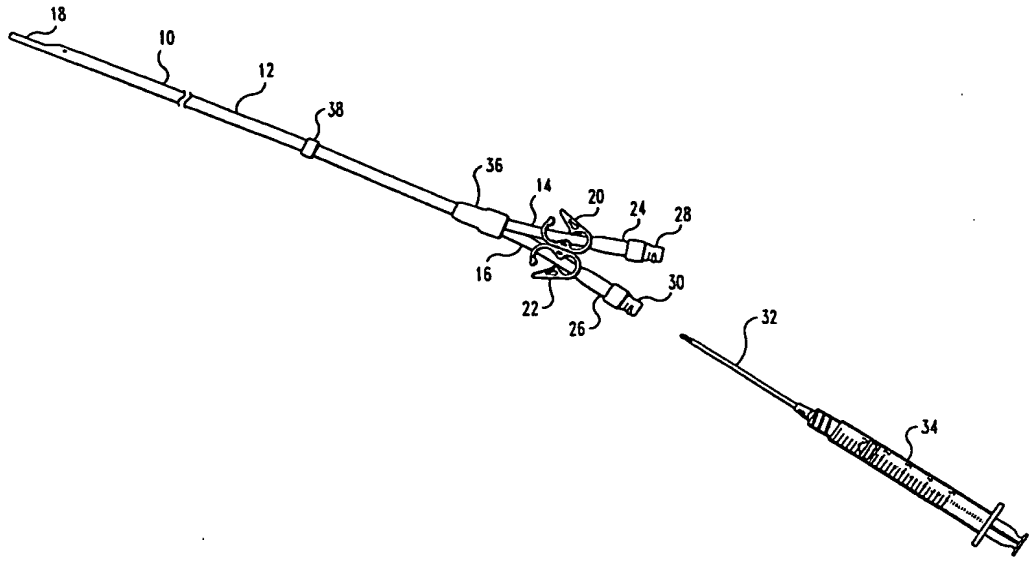
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ASH, Stephen, R. [US/US]; 3736 Pershing Drive, Lafayette, IN 47905 (US).

(74) Agents: COY, Gregory, B. et al.; Woodard, Emhardt, Naughton, Moriarty & McNett, Bank One Center/Tower, Suite 3700, 111 Monument Circle, Indianapolis, IN 46204 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHOD OF ENHANCING CATHETER PATENCY USING A CITRATE SALT CATHETER LOCK SOLUTION



(57) Abstract

This invention relates to an infusion device for a catheter lock solution, to a method of enhancing the patency of catheters in animals and to a catheter lock solution. The device includes a syringe (34) containing a lock solution comprising a citrate salt. The method for enhancing the patency of catheters includes infusing a lumen (14, 16) of an indwelling catheter (10) with a lock solution comprising a citrate salt. In one aspect of the invention, the catheter lock solution includes a citrate salt and a viscosifying agent. The lock solution is prepared to have sufficient viscosity and density to remain in the lumen for a desired amount of time.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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METHOD OF ENHANCING CATHETER PATENCY USING A CITRATE SALT CATHETER LOCK SOLUTION

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of United States Provisional Application Serial No. 60/097,777 filed on August 25, 1998, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention generally relates to intravascular infusion devices and methods of enhancing the patency of intravascular catheters. More specifically but not exclusively, this invention relates to infusing a lock solution into an indwelling intravascular catheter and to methods of inhibiting infection in an animal having an indwelling intravascular catheter.

BACKGROUND OF THE INVENTION

Catheters are used with increasing frequency to treat patients requiring a variety of medical procedures. The catheters offer many advantages for patients; for example, catheters provide ready access without repeated injections for administration of large volumes of fluids, nutrients, medications and withdrawal of blood. The catheters can either be acute or temporary for short-term use or chronic for long-term treatment. They are commonly inserted into central veins (such as the vena cava) from peripheral vein sites. Great care must be taken in the placement and use of a chronic catheter to prevent infection of the patient at the site of access or within the vascular system. Chronic venous catheters usually contain a DACRON cuff attached to the catheter and placed under the skin, which promotes ingrowth of fibrous tissue, fixes the catheter in position, and prevents bacterial migration around the catheter.

Catheters can be used for infusion of fluids, such as, for example, drugs, electrolytes or fluids used in chemotherapy, or for the removal of blood on an intermittent basis. For example, in hyperalimentation treatment, the catheters are usually used for infusion of large volumes of fluids. In chemotherapy, catheters are used for infusion of drugs on an intermittent basis, ranging from daily to weekly. For hemodialysis, dual-lumen catheters are used--usually three times per week; one lumen allows removal of blood, while the other lumen allows blood to return. However, catheters, especially chronic catheters, have drawbacks. They can become occluded by a thrombus, and even if extreme care is

taken, the catheters can increase a patent's risk of infection.

In order to prevent clotting of the catheters between uses, the catheters are usually filled with a lock solution that comprises a concentrated solution of the commonly used anticoagulant, heparin (up to 10,000 units of heparin per catheter lumen). The heparin lock solution is injected into each lumen immediately after each use, and preferably left in the catheter until the catheter is accessed again. The heparin lock solution must be withdrawn from the catheter before the next use because infusing this amount of heparin in a patient might result in excessive bleeding.

However, even with the use of a heparin lock solution, the catheter can become occluded between uses from coagulation of blood in the catheter. Blood may be found in the catheter because, for example, an inadequate volume of heparin was infused within the catheter lumen, the heparin diffused from the lumen, or residual blood remains in the lumen. This often results in formation of a thrombus with concomitant loss of flow through the lumen. The occluded catheters frequently are removed and/or replaced.

Since catheters are inserted into veins or arteries, they bypass the protective dermis layer, and provide direct access to a patient's blood stream. This can cause the inadvertent transfer of infectious agents into the vein or artery at the location of the catheter. In addition, the foreign surfaces of catheters can create a smooth surface at which bacteria can grow, and at which the white cells are unable to surround or "phagocytize" the bacteria.

Heparin has no anti-bacterial properties and, in fact, may help to promote growth of bacteria within the "biofilm" layer of protein on the catheter surfaces (protamine has the opposite effect). The "biofilm" proteins on the catheter surfaces can protect bacteria from antibiotics and white cells. Also, heparin induces the loss of platelets and, paradoxically, can induce clotting in some patients (the "white clot" syndrome). Since catheters, particularly venous catheters, are frequently accessed with syringes, or uncapped and directly connected to IV lines, they have a propensity to become contaminated. If there is bacteremia (bacteria in blood), then the catheter surfaces within the vein or artery can become seeded with bacteria. In either case, the patient can develop septicemia (infection in the blood) and become seriously ill. Often these patients must be hospitalized and given intravenous antibiotics. In spite of this care, patients often remain seriously ill until the infected catheter is removed.

Thus in light of the above described problems, there is a continuing need for advancements in the relevant field, including improved methods, composition and devices relating to enhancing the patency of indwelling intravascular catheters. The present invention is such an advancement and provides a wide variety of benefits and advantages.

SUMMARY OF THE INVENTION

The present invention relates to catheter lock solutiona, intravascular infusion devices for infusing a lock solution into patient and to methods for enhancing the patency of intravascular catheters. Various aspects of the invention are novel, nonobvious, and provide various advantages. While the actual nature of the invention covered herein can only be determined with reference to the claims appended hereto, certain forms and features, which are characteristic of the preferred embodiments disclosed herein, are described briefly as follows.

In one form, the present invention provides a method of treating patients having an indwelling intravascular catheter. The method comprises selecting a patient having an indwelling intravascular catheter defining a lumen therethrough and having an infection or a substantial risk of infection related to the presence of the catheter; and infusing a catheter lock solution into the lumen. The solution comprises a citrate salt solution having a concentration effective to eliminate infection and to reduce the likelihood of subsequent infection. In one embodiment, the citrate salt can be included in the catheter lock solution in a concentration preferably within the range, in weight percent, of about 1.5% to about 50%. The catheter lock solution can include a viscosifying agent such as polyethylene glycol, glycerin, polyglycerin or mixtures thereof. In an alternative embodiment, the lock solution is prepared to have a pH level lower than about 6.5, more preferably between about 4.5 and about 6.5.

In another form, the present invention includes a method of inhibiting infections in an animal having an indwelling catheter defining a lumen therethrough. The method comprises infusing into the lumen a pharmaceutically acceptable lock solution including a compound having anticoagulant and antibiotic activity. The lock solution has a density and a viscosity sufficient to maintain the lock solution in the lumen for a desired amount of time. Preferably the lock solution has a viscosity of from about 1.5 cP to about 4.0 cP. In one embodiment the lock solution includes the citrate salt in a hypertonic concentration, preferably in a concentration between about 1.5 and about 6.5. In another embodiment the lumen of the catheter has an internal volume and a sufficient amount of the lock solution is infused into the lumen, to fill, in percent by volume, between about 80% and about 100% of the internal volume of the lumen.

In yet another form, the present invention provides a method of treating animals that exhibit a risk of infection and having a surgically implanted catheter. The method comprises adding a pharmaceutically acceptable lock solution comprising a bactericidal component into the catheter. The bactericidal component includes greater than about 50 wt%, based on the weight of the bactericidal component, of a citrate salt. In preferred embodiments, the pharmaceutically acceptable lock solution is prepared to be sufficiently caustic to substantially inhibit the growth of bacteria and microorganisms in the lumen.

In still yet another form, the present invention includes an infusion device for infusing a lock solution into a lumen of a catheter. The infusion device includes

a syringe and a catheter lock solution contained in the syringe. The lock solution is preferably a pharmaceutically acceptable solution comprising a citrate salt, and the syringe containing the solution is preferably sterilized. The solution may also include a viscosifying agent to provide to the lock solution sufficient viscosity and density to remain in the lumen for a desired amount of time. In preferred embodiments, the lock solution has a density of between about 1.0 g/ml and about 1.5 g/ml and a viscosity between about 1/5 cP and about 4.0 cP.

In still another form, the present invention provides a kit for accessing a patient's intravascular system. The kit comprises: a catheter defining therethrough at least one lumen; a container; and a catheter lock solution contained within the container, the solution comprising a citrate salt solution.

In yet another from, the present invention provides a catheter lock solution. The lock solution includes, in weight percent, about 1.5% to about 50% of a citrate salt, and an amount of a viscosifying agent sufficient provide the lock solution with a viscosity of from about 1.0 cP to about 4.0 cP.

Further objects, features, aspects, forms, advantages and benefits shall become apparent from the description and drawings contained herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view of one embodiment of a catheter and syringe for infusing a lock solution into a catheter for use with the present invention.

FIG. 2 is a graph plotting monthly incidence of sepsis in all patients of a hemodialysis unit.

FIG. 3 is a graph plotting the number of vials of urokinase used for catheter occlusion per month in a hemodialysis hospital unit.

FIG. 4 is a graph plotting the longevity of one embodiment of a tunnel catheter for use with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to the embodiments illustrated herein and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended. Any alterations and further modifications in the described processes, systems or devices, and any further applications of the principles of the invention as described herein, are contemplated as would normally occur to one skilled in the art to which the invention relates.

In one form, the present invention provides a catheter having retained therein a lock solution. The lock solution enhances the patency of the catheter and exhibits anti-coagulation and antibiotic activity. The lock solution provides particular advantages by increasing the longevity of catheters, reducing incidence of catheter occlusion, and reducing incidence of sepsis or bacterial infection in the patient. In addition, the lock solution of the present invention can be used with or without other anticoagulant agents and/or other antibacterial agents. Further, certain lock solutions of the present invention can be infused into the patient from the catheter in preparation for a subsequent use of the catheter without the necessity of withdrawing the lock solution from the catheter before infusion of additional fluids or medications.

In another form, the present invention provides a method of enhancing the patency of a catheter. The method includes infusing into the catheter a lock

solution selected in accordance with the invention and allowing the lock solution to remain in the catheter for a desired amount of time between catheter uses.

The catheters for use with the present invention typically can either be acute (temporary) or chronic (long-term) catheters surgically implanted in the animal. The catheters usually are inserted into a vein or artery. The catheters are typically used in varying intervals to administer fluids, nutrients, and medications into the body. The catheters also can be used to withdraw body fluids, such as blood, for hemodialysis treatment. When not in use, the catheter remains in its intravascular position until subsequent treatment is preferred

The catheters used accordance with this invention include known and commonly used catheters and are readily available from a variety of commercial sources. The catheters may vary in configuration and size. One type of catheter commonly used in accordance with this invention is a tunneled catheter that includes a cuff for ingrowth of tissue to anchor the catheter. Examples of catheters that may be used include, but are not restricted to, an ASH SPLITCATH by Ash Medical of West Lafayette, Indiana; TESIO and ASH CATHETERS by Medcomp of Harleysville, Pennsylvania; PERM CATH by Quinton Instrument Company of Seattle, Washington; HICKMAN and VAS CATH by Bard, Inc. of Salt Lake City, Utah. Catheters containing totally subcutaneous ports are also useful in the present invention; examples include LIFESITE by Vasca of Topsfield, Maine, and DIALOCK by Biolink, Inc. of Boston, Massachusetts.

FIG. 1 depicts one example of a catheter 10 for use with this invention. Catheter 10 is a dual lumen catheter and includes an outer sheath 12 having a cuff 38

and first and second lumens 14 and 16, respectively. Lumens 14 and 16 extend from distal tip 18 through sheath 12 and exit from sheath 12 at connection 36. Each of lumens 14 and 16 include releasable clamps 20 and 22, respectively. Each of lumens 14 and 16 terminate in a threaded end 24 and 26, which can be threadedly attached to protective end caps 28 and 30, respectively. Fluids including a lock solution can be infused or withdrawn from each lumen 14 and 16 by inserting needle 32 of a syringe 34 through protective end caps 28 and/or 30 after protective end caps 28 and/or 30 have been sterilized by cleaning successively, for example with betadine and alcohol. Alternatively, one or both protective end caps 28 and 30 can be removed and threaded ends 24 and 26 can be threadedly attached via a connector (not shown) to lines for infusion or withdrawal of fluids (not shown). Once a desired treatment session has been completed, the needles are removed or the connectors are replaced with fresh, sterile protective end caps. The lumens are then typically flushed with normal saline, after which a lock solution is injected into each lumen. All procedures are performed using standard sterile techniques well known to those skilled in the art. The catheters for use with this invention can be prepared from a variety of materials, including, for example, silicon, polyurethane, polyvinyl, silicone, or silastic elastomer.

Chronic catheters are usually inserted through an internal jugular vein into the superior vena cava. Usually these catheters include a cuff attached to the exterior of the catheter and placed under the skin, which promotes ingrowth of fibrous tissue, and thus fixes the catheter in position and prevents bacterial migration around the catheter. While the catheters are

manufactured to function for several months, for example, TESIO catheters can last for up to four years with proper intervention, in actual practice, the catheters, prior to the present invention, have exhibited limited longevity because of occlusion and/or infection. These catheters frequently must then be removed and/or replaced.

As mentioned above, in order to prevent clotting of catheters between use, catheters are commonly filled with lock solutions comprising an anticoagulant agent and sometimes a second agent having antibacterial properties. It has unexpectedly been determined that citrate salt solutions as described herein exhibit surprisingly effective antibacterial activity. In a series of tests, with a variety of bacterium spores injected into a 47% solution of citrate salts, a six-log kill is obtained in seven days for E.coli and P.aeruginosa, and in 21 days for S.Aureus.

In accordance with the invention a catheter lock solution comprising a citrate salt is used to increase the patency of implanted catheters. As used herein, the term "lock solution" refers to a solution that is injected or otherwise infused into a lumen of a catheter and with the intention of allowing a substantial portion of a lock solution to remain in the lumen until it is desired or required to access that particular lumen again, typically for additional treatment, i.e., infusion or withdrawal of fluid. Preferably the lock solution can remain in the lumen for a desired amount of time lasting from about 1 hour to 3 or 4 days or longer. However, frequently the lock solution is changed on a daily basis during regular care and sterile maintenance of the indwelling catheter. Use of a lock solution of the present invention provides particular advantages for

patients with catheters by prolonging the lifetime of the catheter, lengthening the interval between required replacements of the lock solution and inhibiting infections in the patient.

In one form, the lock solution of the present invention comprises an amount of a citrate salt to provide an effective catheter lock solution, preferably, but not exclusively, a hypertonic lock solution. The term hypertonic is used herein to refer to a fluid having an osmotic concentration and a density greater than the osmotic concentration and density of the blood of the patient. The lock solution preferably comprises a citrate salt with a concentration range, in weight percent, of from about 1.5% to about 50% with an osmolality of about 300 to about 6400 mOsm. More preferably, the lock solution comprises citrate salt in a concentration range of from about 10% to about 40%, yet more preferably, in a concentration range of from about 20% to about 30%.

In preferred embodiments, the lock solution comprises a citrate salt, and the lock solution is prepared to have sufficient viscosity and density to remain in the lumen for a desired amount of time. It is well known that catheters are manufactured to have a variety of configurations and lumen diameters. For example, catheters can include single or double lumens. The double lumens can be fused adjacent to each other or they can be concentric. The lumens can have varying cross-sectional areas and shapes, ranging from substantially circular to substantially ovoid. A phenomenon common to most lock solutions is that a portion of the solution at the distal end of the lumen diffuses into the patient's blood stream and is replaced in the catheter by blood.

While not intending to be bound by any theory, it is thought that the rate of diffusion of a lock solution from a lumen can be influenced by the cross-sectional shape and area of the particular lumen(s), the density of the lock solution, and the viscosity of the lock solution. Typically, high density lock solutions tend to fall out of the lumen of the catheter, allowing blood to enter into the lumen.

A lock solution of the present invention is preferably prepared to have a viscosity and density such that a substantial portion of the lock solution does not diffuse or flow out of a catheter lumen within about 8 hours. More preferably, the lock solution of the present invention does not diffuse out of a lumen to a substantial extent within about 12 hours, still more preferably within about 24 hours.

In a preferred aspect of the invention, the lock solution of the invention is prepared to have a selected density of from about 1.02 g/ml to about 1.04 g/ml and a viscosity of from about 1.5 centipoise (cP) to about 4.0 cP. More preferably the lock solution has a density of from about 1.02 g/ml to about 1.03 g/ml and a viscosity of from about 1.5 cP to about 2.0 cP. For example in a 10 French TESIO catheter studies with sodium citrate solutions, 46.7% by weight citrate with density of 1.025 and viscosity of 2.0 (by gravity viscometer) where found to remain within the cylindrical catheter for 3 days or more, with the catheter suspended in a solution having viscosity of blood, 13 cP at 37°. In catheters such as the SPLITCATH, with lumens having less hydraulic resistance, this solution will exit the catheter due to gravitational forces. A catheter lock solution

comprising 23% by weight citrate, however, will remain in place for 3 days or more.

The density of the lock solution can be varied by varying the amount of salts included in the solution, with 46.7% being appropriate for 10 French cylindrical catheters, and 23% being appropriate for the double-D shaped lumens of the SPLITCATH.

The viscosity of the lock solution can be varied by adding a viscosifying agent. Viscosifying agents useful with the present invention include those pharmaceutically acceptable agents known or commonly used in treatment of animals including humans. Examples include, but are not limited to, polyethylene glycol, glycerin, polygeline, and non-metabolizable sugars such as sorbitol and mannitol and mixtures of these compounds. An excellent aspect of the invention, therefore is a composition useful as a lock solution that comprises a citrate salt and a viscosifying agent. The viscosifying agent allows a higher concentration of citrate to be used without having egress of the lock solution from the catheter due to high density of the lock solution.

While is understood that optimal viscosity and density are dependent upon the shape and size of a particular lumen, a person of ordinary skill in the art, in view of the description herein, can readily determine a desired density and viscosity for a particular catheter without undue experimentation.

In a preferred embodiment, the lock solution is prepared to have a pH lower than that of the pH of the patient's blood. For example, in humans, the lock solution may advantageously be prepared to have a pH lower than about 6.5, more preferably, the lock solution is prepared to have a pH level of from about 4.5 to about

6.5. Still yet more preferable, the lock solution is prepared to have a pH level of from about 5.0 to about 6.5. The lower the pH, the greater the antibacterial effect of the citrate and the greater the caustic activity in dissolving clots. The pH of the catheter lock solution can be varied by adding either an acid or base according to methods known to those skilled in the art. For example, the pH of the catheter lock solution can be lowered by including a sufficient amount of citric acid to the solution to provide the desired pH level.

An inventive lock solution can be prepared to include a variety of other pharmaceutically acceptable agents. For example, the lock solution can include salts, such as, for example, sodium chloride and sodium heparin. The lock solution can also include a variety of other antibacterial, antimicrobial and anticoagulant agents. Such antibacterial and antimicrobial agents are well known to those skilled in the art and can include, without limitation, gentamicin, vancomycin, and mixtures of these agents. Additional anticoagulant agents include, for example heparin, urokinase, tissue plasminogen activation (tPA) and mixtures of these agents.

By "pharmaceutically acceptable", it is meant that the lock solution and the included salts and other additives which are, within the scope of sound medical judgment, suitable for use in contact with tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with the reasonable benefit/risk ratio. It is also typically necessary that a composition be sterilized to reduce the risk of infection. For example, pharmaceutically acceptable salts are well-known in the

art, for example, as found in S.M. Berge et al. described in detail in *J. Pharmaceutical Science*, 66:1-19, 1977.

In yet another form, the present invention provides a method of inhibiting infections in animals having an indwelling intravascular catheter. A compound having anticoagulant and antibacterial activity is selected, for example, the citrate salt such as trisodium citrate. A lock solution is prepared, including the compound having anticoagulant and antibacterial activity. The resulting lock solution is then infused into the lumen or a catheter.

Thus, the lock solution of the present invention including a citrate salt can be prepared and further include a bactericidal component. In a preferred embodiment, the bactericidal component includes greater than 50% by weight based on the weight of the bactericidal component of the citrate salt. More preferably, the bactericidal component includes greater than about 75%, by weight based on the weight of the component, of the citrate salt. Still more preferably, the bactericidal component includes greater than about 90% of a citrate salt.

Once a lock solution is infused into the lumen of the catheter, it is allowed to remain until that particular catheter or lumen is desired to be accessed again. The lock solution can be flushed directly into the patient without the necessity of removing the fluid before infusing fluids for subsequent treatment. Alternatively, the lock solution can be removed from the catheter prior to infusion or removal of additional fluid for further treatment.

When the lock solution of the present invention is injected into the lumen of the catheter, a sufficient

amount of the lock solution can be injected to substantially fill the lumen of the catheter. Alternatively, a volume less than the amount of fluid needed to fill the catheter can be injected into the lumen. For example, a sufficient amount of lock solution can be injected into the catheter to fill about 80 to about 100% of the internal volume of the catheter. In yet another embodiment, an amount greater than the internal volume of the catheter can be injected. For example, an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the catheter can be injected into the lumen, without adverse effects on the clotting system of the patient.

In yet another embodiment, the lock solution of the present invention can be infused into the lumen or lumens of the indwelling catheter of patients exhibiting a risk of infection. Surgically implanted catheters are used in the treatment of patients exhibiting a variety of health problems. It is well known that certain health problems and/or patients exhibit increased risk of infection based upon historical observation by those skilled in the art. The present invention provides distinct advantages when used on those patients having an increased risk of infection by inhibiting infection in those patients.

In another embodiment, patients are screened for an infection or a substantial risk of infection related to the presence of the catheter. For those patients having such an infection or substantial risk of infection, a catheter lock solution prepared according to the present invention is infused into the lumen of the catheter. The catheter lock includes a citrate salt in a concentration effective to eliminate the

infection and/or reduce the likelihood of subsequent infection.

A lock solution of the present invention has other advantages besides antibacterial properties. If infused into a patient, citrate in the lock solution will be inactivated by calcium in the blood or calcium derived from body stores. When a lock solution having a hypertonic citrate concentration of 47% is used, the total amount of citrate in the lock solution contained in one lumen of a tunneled catheter is approximately 2 ml, containing 3.4 mM of sodium citrate. This amount of citrate is equal to the amount of calcium contained in 1.5 liters of blood. If infused rapidly, this amount of citrate could cause transient hypocalcemic symptoms, but would not anticoagulate the patient. Therefore, if a tunneled catheter is used for fluid infusion for a patient in the emergency room or operating room, the patient will not become anticoagulated just at the time when blood coagulation is important.

In alternative forms the present invention provides a catheter lock infusion device. The infusion device comprises a syringe containing a lock solution prepared according to the present invention. In yet another form the present invention also includes a kit for accessing a patient's intravascular system. The kit includes a catheter having at least one lumen. A container of a catheter lock solution that was prepared according to the present invention is included in the kit. In one embodiment the lock solution includes a viscosifying agent dissolved or dispersed in the lock solution.

For the purpose of promoting further understanding and appreciation of the present invention and its advantages, the following Example is provided. It will be understood, however, that this Example is illustrative and not limiting in any fashion.

Example Illustrating Use of Lock Solutions containing Citrate Salts:

Methods

A study utilizing concentrated citrate in the catheter lock solution was performed on an outpatient dialysis unit (RTC) with 60% of patients having chronic central venous catheters (50 catheters total, the majority ASH SPILTCATH and the remaining TESIO and HICKMAN catheters). At four-month intervals, the citrate concentration in the lock solution was increased from 10% to 20% to 47%. Gentamicin was added at 3 mg/ml to the 10% and the 20% solutions, but not to the 47% citrate solution. The overall incidence of bacteremia in the unit was followed and the amount of urokinase used to open occluded or low-flowing catheters was recorded. The results were compared in incidences of bacteremia and use of urokinase in the unit before the implementation of the lock solution containing citrate salts.

Starting in 1994, all episodes of bacteremia in the outpatient hemodialysis unit were monitored and recorded. Episodes were totaled each month, for all patients, for patients with and without tunneled central venous catheters, and for patients with and without catheter-related explanations for bacteremia. The incidence of bacteremia was calculated as the percent of patients in the unit developing bacteremia

per month ("1%"=1 bacteremic episode per 100 patients in the unit for one month, or 3.3 episodes per 1000 patient-months). The incidence was graphed each month, for the entire period since 1994.

During the period from January 1998 to July 1999, there were 70 patients in this unit, with approximately 60% having tunneled central venous catheters for chronic dialysis (40 catheters total). At the start of the study, the most prevalent catheter in the unit was the Medcomp twin TESIO, though there were a few Bard SOFT CELL catheters. Starting in January 1998, the Medcomp ASH SPLITCATH catheter became the standard tunneled catheter placed in patients beginning dialysis or needing catheter replacement. Almost all of these tunneled catheters were placed using the SITE-RITE ultrasound device for IJ localization. These catheters routinely provided an average blood flow near 300 ml/min.

The average monthly incidence of positive blood cultures in the unit was calculated for the time period from January 1998 through July 1998. During this time period, heparin was used as the standard catheter lock solution, with either 5,000 units or 10,000 units instilled into each lumen at exactly the catheter volume. The incidence of bacteremia during this period was 4.6%, which was higher than the average level since 1994. In August 1998, hemodialysis patients were informed of the plan to change from heparin to sodium citrate/gentamicin as the standard anticoagulant lock for tunneled catheters. From September to December 1998, 10% citrate with 3 mg/ml gentamicin was used as standard catheter lock, injecting slightly more than the catheter volume (2.5 ml total). From January 1999 through April 1999, 20% citrate with 3 mg/ml gentamicin

was the standard catheter lock, injecting slightly more than the catheter volume (2.5 ml total). From May 1999 to July 1999, 47% citrate was the standard catheter lock, injecting exactly the catheter volume. All citrate solutions were made from 47% stock solution, used straight from the 30 ml bottle or in combination with saline and gentamicin. (46.7% trisodium citrate, "triCitrasol", Citra Anticoagulants, Inc., distributed by Ash Medical Systems, West Lafayette, IN). Patients were closely monitored for any evidence of adverse reactions each time the citrate concentration was increased. The monthly incidence of bacteremia was calculated for the 10-month period during which citrate/gentamicin or 47% citrate was used for catheter lock, and compared to the baseline 7-month period by Two-tailed T Test (assuming equal variances).

Also during this time period, the unit use of urokinase (Abbott Laboratories) was monitored. The number of vials of urokinase use by the RTC unit was calculated on a monthly basis. The total number of vials ordered and used by the unit each month in the period from January 1998 through July 1998 was compared to the number of vials used after the conversion to citrate, from September 1998 to July 1999. After May 1999, urokinase became unavailable, but before this time it was available on request. The number of vials used per month in the baseline period was compared to the number of vials after implementation of citrate/gentamicin or 47% citrate catheter lock, by Two-tailed T Test (assuming equal variances).

During the study period, the longevity of tunneled catheters was also investigated, since the prevention of infection of tunneled catheters is less important if

other factors such as clotting or sheath formation limit the life of the catheters. All Ash SPLITCATH catheters placed in end-stage renal disease (ESRD) patients after January 1998 (including patients in two satellite outpatient units) were evaluated and the longevity of the catheters was determined. In all, 57 Splitcath catheters were placed in 57 patients. Failure was defined as any catheter being removed for any complication, whether due to infection or obstruction of flow. Longevity of catheters was determined using lifetable analysis.

Since the outpatient unit has many patients with tunneled catheters, nurses and technicians use utmost care in opening the catheters and connecting to dialysis machines. The caps of the catheter are soaked in betadine for 5 minutes before the caps are removed. Nurses and technicians wear masks and gloves, and the patient wears a mask when the catheter is opened. New protective caps are placed on the catheter following each procedure. Catheters and connectors are inspected for leaks or evidence of damage, each treatment.

Incidence of Bacteremia

The incidence of bacteremia in all 70 patients at the RTC unit was 4.5% of patients per month during the baseline period from January through July of 1998. Following the implementation of hypertonic citrate/gentamicin and then 47% citrate as catheter lock, the incidence of bacteremia decreased significantly to 1.2% (Figure 2, $P<0.001$). There was a downward trend in bacteremia as concentration of citrate was increased from 10 to 20 to 47%. In the

last three months of the study, when 47% citrate was used, the incidence of bacteremia has been zero.

Utilization of Urokinase

The use of urokinase in the dialysis unit during the baseline period was 41 vials per month, or approximately 1 vial per patient with tunneled catheter per month. After implementation of hypertonic citrate/gentamicin then 47% citrate as catheter lock, the use of urokinase decreased to 20 vials per month, about ½ vial per patient with tunneled catheter per month (Figure 3, P=0.02). During the last three months of this study (May, June, July 1999), no urokinase was used for any catheter. In June and July of 1999, urokinase was unavailable at the hospital, and the hospital had not yet substituted syringes of tissue plasminogen activator (tPA) for catheter infusion. However, no catheters were completely occluded or removed for flow problems during these months, so it did not appear that urokinase was required in this month.

Catheter Survival

During the period from January 1998 to July 1999, 57 ASH SPLITCATH catheters were placed in 57 patients in the RTC and satellite units, with an average follow-up of 8 months. One small satellite unit continued using heparin for anticoagulant catheter lock, while the other followed the RTC protocol of increasing citrate catheter lock concentration. During this period, catheters without signs of infection were not removed for bacteremia, but only in patients in whom antibiotic therapy failed to clear signs of infection within 24 hours. Only 3 of the 57 catheters were

removed, 2 for concomitant infection which failed to clear, and one for decreased blood outflow rate. The lifetable analysis of longevity of these catheters indicates a 95% survival at one year (Figure 4). Interventions in these catheters were few, and as discussed above, urokinase use was decreased as hypertonic citrate/gentamicin or 47% citrate were used as catheter lock. Mean catheter flow rate for the Splitcath® catheter remained approximately 300 ml/min during the study, with venous and arterial pressures below 250 mmHg (the pre-defined limit for pressures in these dialysis units).

Conclusions/Discussion

In this study of tunneled catheters in a single dialysis unit, hypertonic citrate (10 or 20%) in combination with gentamicin, or 47% citrate are at least as effective as heparin in preventing clotting of the catheters. The use of urokinase to open these tunneled catheters does not increase, and in fact significantly decreases after implementation of the citrate catheter lock solutions.

Hypertonic citrate as catheter lock appears to decrease the incidence of bacteremia in a dialysis unit with a high percentage of patients with tunneled catheters. When catheters are locked with 10% or 20% citrate containing 3 mg/ml gentamicin, the incidence of bacteremia decreases significantly. An even greater decrease in incidence of bacteremia appears to occur with use of 47% citrate alone (without gentamicin). Through a variety of actions, concentrated citrate is bactericidal and sporicidal when tested in vitro. Therefore, it is expected that it would diminish the

bacterial content of catheters after chance contamination of the catheter hub. On the other hand, a similar antibacterial effect could be obtained through the effect of citrate on biofilm; if the mild corrosive action of citrate helps to eliminate the biofilm, it would also eliminate bacteria trapped within the biofilm. The effect of citrate on bacterial contamination of catheters can decrease risk of bacteremia in patients with catheters without the risk of developing resistant strains of the bacteria (as will occur with antibiotic lock solutions).

Of course, with proper care it is possible to utilize tunneled catheters for dialysis without an antibacterial solution infused. In a satellite outpatient hospital dialysis unit, 20 stable ESRD patients are dialyzed, and the percentage and types of catheters (60% of patients, mostly having mostly SPLITCATH catheters and some TESIO catheters) are similar to those at the RTC unit. The unit uses the same precautions as the RTC unit in handling tunneled catheters. As opposed to the RTC, this unit has traditionally had a very low to zero incidence of bacteremia from any cause. In the period of January 1998 to May 1999, this unit continued to use heparin as catheter lock solution, and had only one patient with bacteremia during this period (representing 5% of all patients, for one month). For all other months the incidence of bacteremia remained zero. Urokinase use also remained low during the entire period.

The problems of infection and occlusion of tunneled catheters for dialysis are paralleled by the smaller catheters used in hospitalized patients with central venous catheters, and in home patients with

long-term TPN, chemotherapeutic and antibiotic administrations. Concentrated citrate may also provide significant advantages in these patients, avoiding catheter clotting, infection and subsequent bacteremia.

The present invention contemplates modification to the infusion device and method of treating patients as would occur to those skilled in the art. It is also contemplated that processes embodied in the present invention can be altered, rearranged, substituted, deleted, duplicated, combined, or added to other processes as would occur to those skilled in the art without departing from the spirit of the present invention. In addition, the various stages, procedures, techniques, phases, and operations within these processes may be altered, rearranged, substituted, deleted, duplicated, or combined as would occur to those skilled in the art. All publications, patents, and patent applications cited in this specification are herein incorporated by reference as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference and set forth in its entirety herein.

Further, any theory of operation, proof, or finding stated herein is meant to further enhance understanding of the present invention and is not intended to make the scope of the present invention dependent upon such theory, proof, or finding.

While the invention has been illustrated and described in detail in the drawings and foregoing description, the same is considered to be illustrative and not restrictive in character, it is understood that only the preferred embodiments have been shown and described and that all changes and modifications that come within the spirit of the invention are desired to be protected.

What is claimed is:

1. A method for treating a patient, comprising:

selecting a patient having an indwelling intravascular catheter defining a lumen therethrough and having an infection or a substantial risk of infection related to the presence of the catheter;

infusing a catheter lock solution into the lumen, the solution comprising a citrate salt solution having a concentration effective to eliminate infection and to reduce the likelihood of subsequent infection.

2. The method of claim 1 wherein the lock solution comprises a citrate salt in a concentration range, in weight percent, of between about 1.5% and about 50%.

3. The method of claim 2 wherein the lock solution comprises a citrate salt in a concentration range, in weight percent, of between about 10% and about 40%.

4. The method of claim 3 wherein the lock solution comprises a citrate salt in a concentration range, in weight percent, of between about 20% and about 30%.

5. The method of any of claims 1-4 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

6. The method of any of claims 1-5 wherein the lock solution has a pH level between about 4.5 and about 6.5.

7. The method of any of claims 1-6 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

8. The method of any of claims 1-7 wherein the catheter has an internal volume and said adding includes injecting the catheter with an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

9. A method of inhibiting infections in an animal having an indwelling catheter defining at least one lumen therethrough, said method comprising infusing into the lumen a pharmaceutically acceptable lock solution including a compound having anticoagulant and antibiotic activity, wherein said lock solution has a density and a viscosity sufficient to maintain the lock solution in said lumen for a desired amount of time, wherein the desired amount of time is at least about 8 hours.

10. The method of claim 9 wherein the lock solution includes a citrate salt in a hypertonic concentration range, in weight percent, of between 1.5% and 50%.

11. The method of claim 10 wherein the lock solution includes a citrate salt in a concentration range, in weight percent, of between 10% and 40%.

12. The method of claim 11 wherein the lock solution includes a citrate salt in a concentration range, in weight percent, of between 20% and 30%.

13. The method of any of claims 9-12 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline or mixtures thereof.

14. The method of any of claims 9-13 wherein the lock solution has a density of between about 1.02 g/ml to about 1.04 g/ml and a viscosity of between about 1.5 cP and about 4.0 cP.

15. The method of any of claims 9-14 wherein the lock solution has a density of between about 1.02 g/ml and about 1.03 g/ml a viscosity of between about 1.5 cP and about 2.0 cP.

16. The method of any of claims 9-15 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

17. The method of any of claims 9-16 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of

the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

18. The method of any of claims 9-17 wherein the lock solution has a pH level between about 4.5 and about 6.5.

19. A method of treating animals having a surgically implanted catheter, said method comprising infusing into said catheter a pharmaceutically acceptable lock solution comprising a bactericidal component, said bactericidal component including greater than about 50%, by weight based on the weight of the bactericidal component, of a citrate salt.

20. The method of claim 19 wherein the bactericidal component includes greater than about 75%, by weight based on the weight of the bactericidal component, of a citrate salt.

21. The method of claim 19 or 20 wherein the bactericidal component includes greater than about 90%, by weight based on the weight of the bactericidal component, of a citrate salt.

22. The method of any of claims 19-21 wherein the lock solution includes a viscosifying agent.

23. The method of any of claims 19-22 wherein the pharmaceutically acceptable lock solution has a pH between about 4.5 and about 6.5.

24. The method of any of claims 19-23 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution sufficient to fill between about 80% and about 100% of the internal volume of the lumen.

25. The method of any of claims 19-24 wherein the lumen of the catheter has an internal volume and said infusing includes infusing the lumen with an amount of the lock solution greater than or equal to about 1.1 times the internal volume of the lumen.

26. An infusion device for infusing a lock solution into a lumen of a catheter, said device comprising:

a syringe;

a pharmaceutically acceptable lock solution contained within the syringe, said lock solution comprising a citrate salt;

wherein said syringe containing the lock solution is sterilized.

27. The device of claim 26 wherein said lock solution comprising a citrate salt.

28. The device of claim 26 or 27 wherein the lock solution comprises a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

29. The device of any of claims 26-28 wherein the lock solution has a density of between about 1.0 and about 1.5 and a viscosity of between about 1.5 cP and 4.0 cP.

30. A device comprising:

an intravascular catheter having at least one lumen; and

a pharmaceutically acceptable lock solution positioned within the lumen, said lock solution comprising a citrate salt, wherein said lock solution has a pH level below about 6.5.

31. The device of claim 30 wherein said citrate salt comprises a sodium citrate salt.

32. The device of claim 30 or 31 wherein the lock solution has a pH level between about 4.5 and about 6.5.

33. The device of any of claims 30-32 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

34. The device of any of claims 30-33 wherein the lock solution has a density between about 1.0 and about 1.5 and a viscosity between about 1.5 cP and about 4.0 cP.

35. A kit for accessing a patient's intravascular system, comprising:

a catheter defining therethrough at least one lumen;

a container; and

a catheter lock solution contained within the container, the solution comprising a citrate salt solution.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19307

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01M 59/00; A61M 5/32
US CL :424/600; 604/265

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/600, 722; 523/122; 604/28, 265

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,364,929 A (SASMOR et al.) 21 December 1982, Abstract.	1-43
A	US 4,677,143 A (LAURIN et al.) 30 June 1987, col. 2, line 50 to col. 3, line 13.	1-43
A, P	US 5,843,016 A (LUGNANI et al.) 01 December 1998, Abstract, and col. 12, lines 47-50.	1-43

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 OCTOBER 1999	Date of mailing of the international search report 22 NOV 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON ELIZABETH FINKEL Telephone No. (703) 305-0154

Form PCT/ISA/210 (second sheet)(July 1992)*

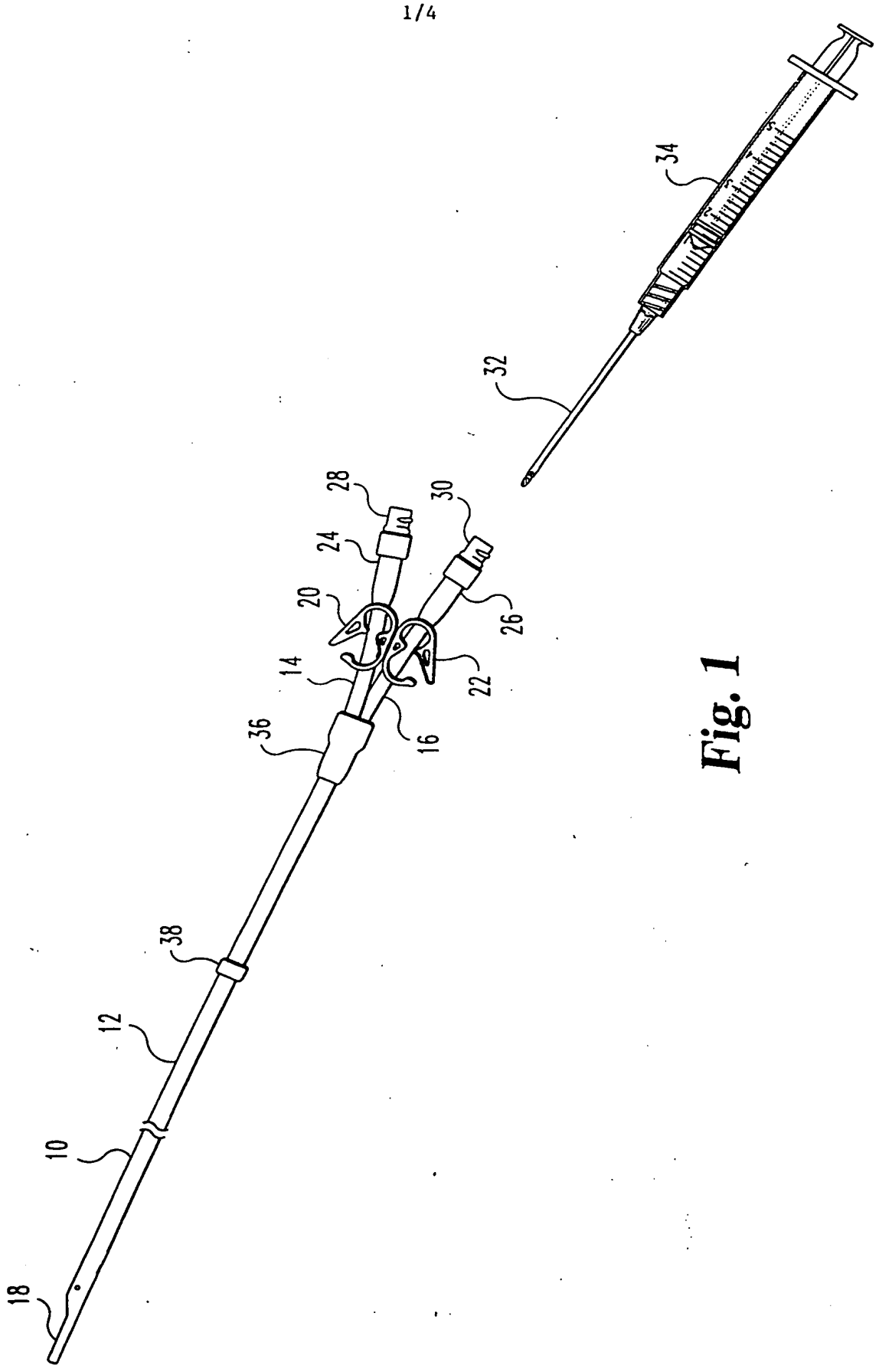
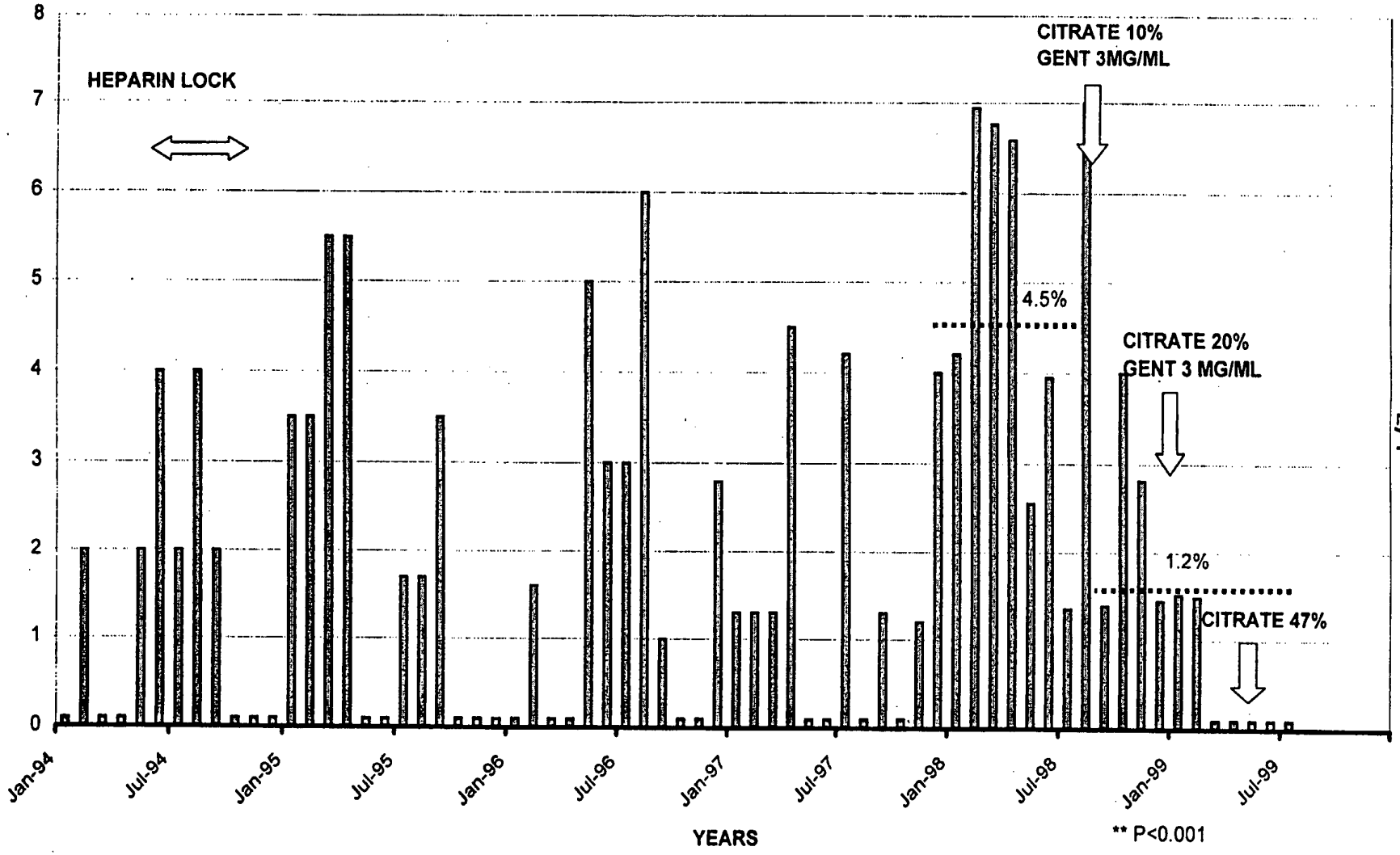


Fig. 1

FIGURE 2

MONTHLY INCIDENCE OF SEPSIS IN ALL PATIENTS, RTC UNIT



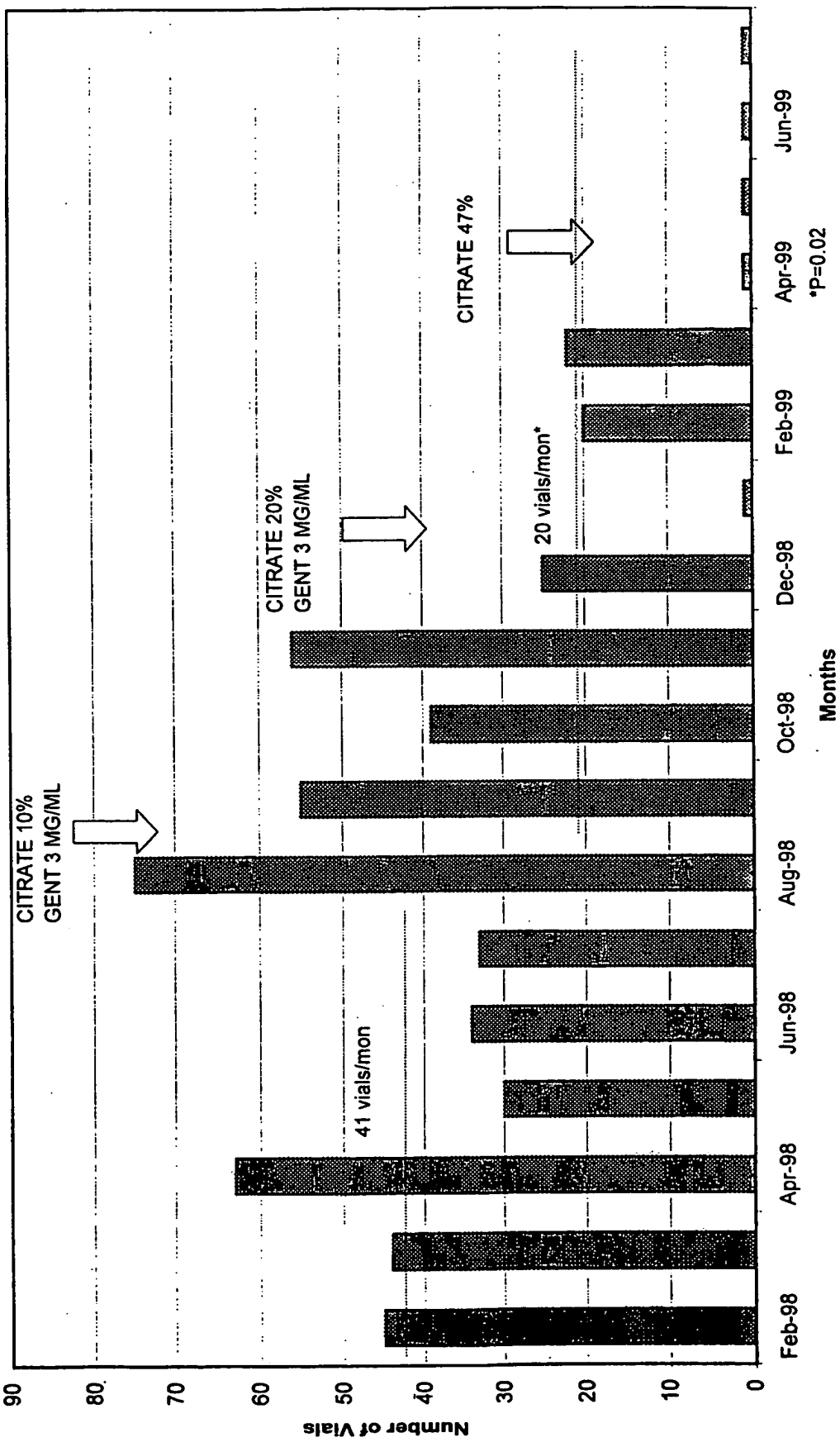
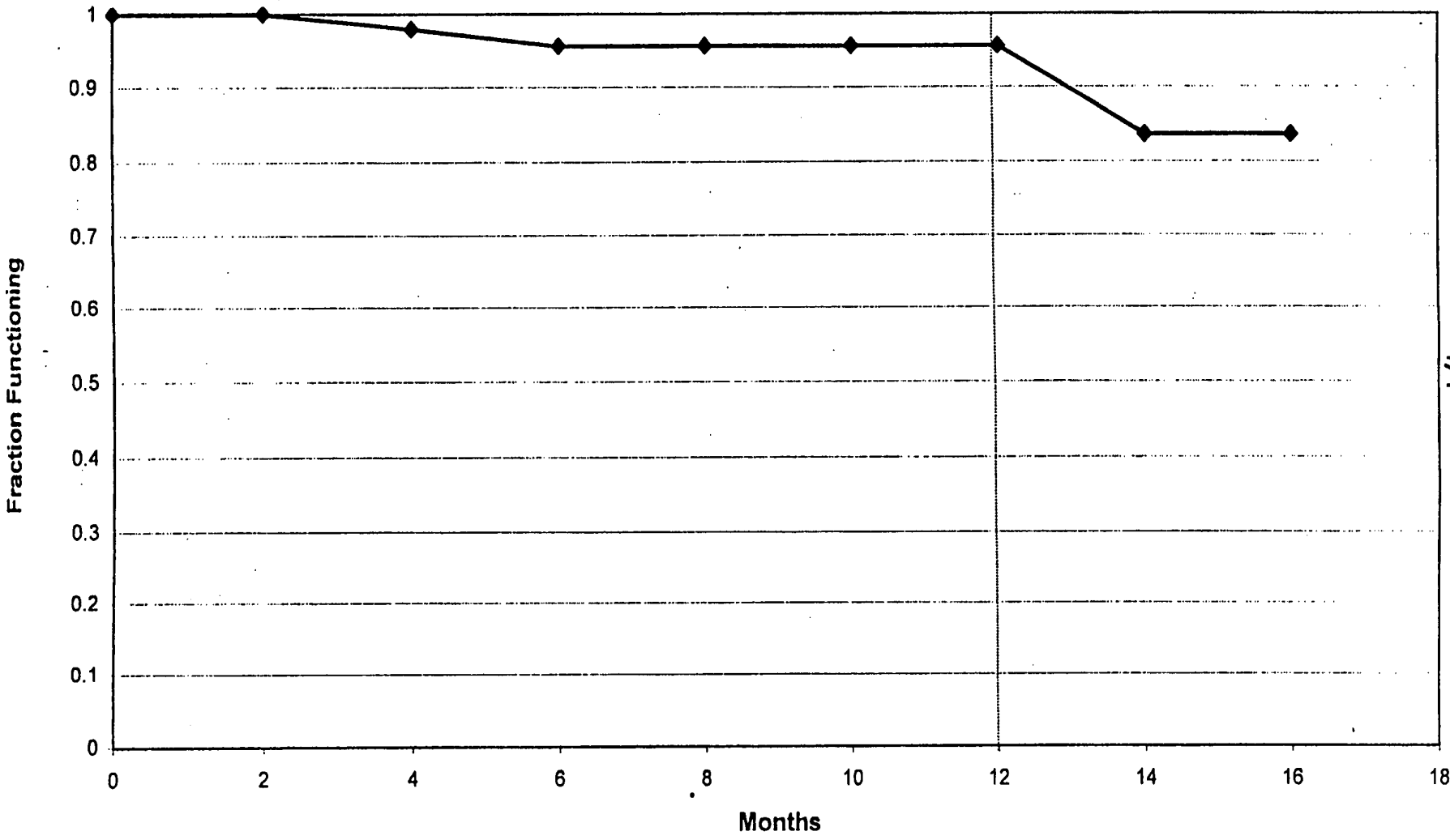


Figure 3

Vials of Urokinase Used For Catheter Occlusion

FIGURE 4
Longevity of Splitcath Catheters



30. A device comprising:

an intravascular catheter having at least one lumen; and

a pharmaceutically acceptable lock solution positioned within the lumen, said lock solution comprising a citrate salt, wherein said lock solution has a pH level below about 6.5.

31. The device of claim 30 wherein said citrate salt comprises a sodium citrate salt.

32. The device of claim 30 or 31 wherein the lock solution has a pH level between about 4.5 and about 6.5.

33. The device of any of claims 30-32 wherein the lock solution includes a viscosifying agent selected from polyethylene glycol, glycerin, polygeline and mixtures thereof.

34. The device of any of claims 30-33 wherein the lock solution has a density between about 1.0 and about 1.5 and a viscosity between about 1.5 cP and about 4.0 cP.

35. A kit for accessing a patient's intravascular system, comprising:

a catheter defining therethrough at least one lumen;

a container; and

a catheter lock solution contained within the container, the solution comprising a citrate salt solution.

36. The kit according to claim 35 wherein said container is a syringe.

37. A catheter lock fluid comprising an aqueous solution of a citrate salt and a viscosifying agent dissolved or dispersed in the solution.

38. The fluid according to claim 37 wherein the viscosifying agent is selected from the group consisting of polyethylene glycol, glycerin, polygeline and mixtures thereof.

39. A composition comprising an aqueous lock solution including, in weight percent, about 1.5% to about 50% of a citrate salt, and an amount of a viscosifying agent sufficient provide the lock solution with a viscosity of from about 1.0 cP to about 4.0cP.

40. The composition of claim 39 wherein the lock solution has a pH level between about 4.5 and about 6.5.

41. The composition of claim 39 or 40 wherein the lock solution includes, in weigh percent, about 10% to about 40% of the citrate salt.

42. The composition of any of claims 39-41 wherein the citrate salt is trisodium citrate.

43. The composition of any of claims 39-42 comprising heparin.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 110209-ASH	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/19307	International filing date *(day/month/year)* 25 AUGUST 1999	Priority date *(day/month/year)* 25 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61M/31/00; and US Cl.: 604/523		
Applicant ASH MEDICAL SYSTEMS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☑ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24 MARCH 2000	11 DECEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON KENNEDY Telephone No. (703) 305-0154

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/19307

I. Basis of the report

1. With regard to the elements of the international application: *

☐ the international application as originally filed

☒ the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages (See Attached), as originally filed
pages _____, as amended (together with any statement) under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/19307

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-43	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-43	YES
	Claims	None	NO
Industrial Applicability (IA)	Claims	1-43	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-43 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the device and/or the lock solution as claimed. Claims 30-34 and 36 are recently allowed because the prior art does not teach the claimed pH. It is known that a blood pH below 6.8 will cause death, thus, it is unlikely that Antwiler would infuse a solution having a pH lower than 6.5 into the blood steam. Claim 35 is recently allowed because Antwiler does not disclose or suggest the viscosifying agent.

---------- NEW CITATIONS ----------

US 5,665,061 A (ANTWILER) 09 September 1997, Abstract, and col. 3 lines 46-59.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-27, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) 28-32, 34, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Page 33, filed with the letter of 13 November 2000.

This report has been drawn on the basis of the drawings,
page(s) 1-4, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

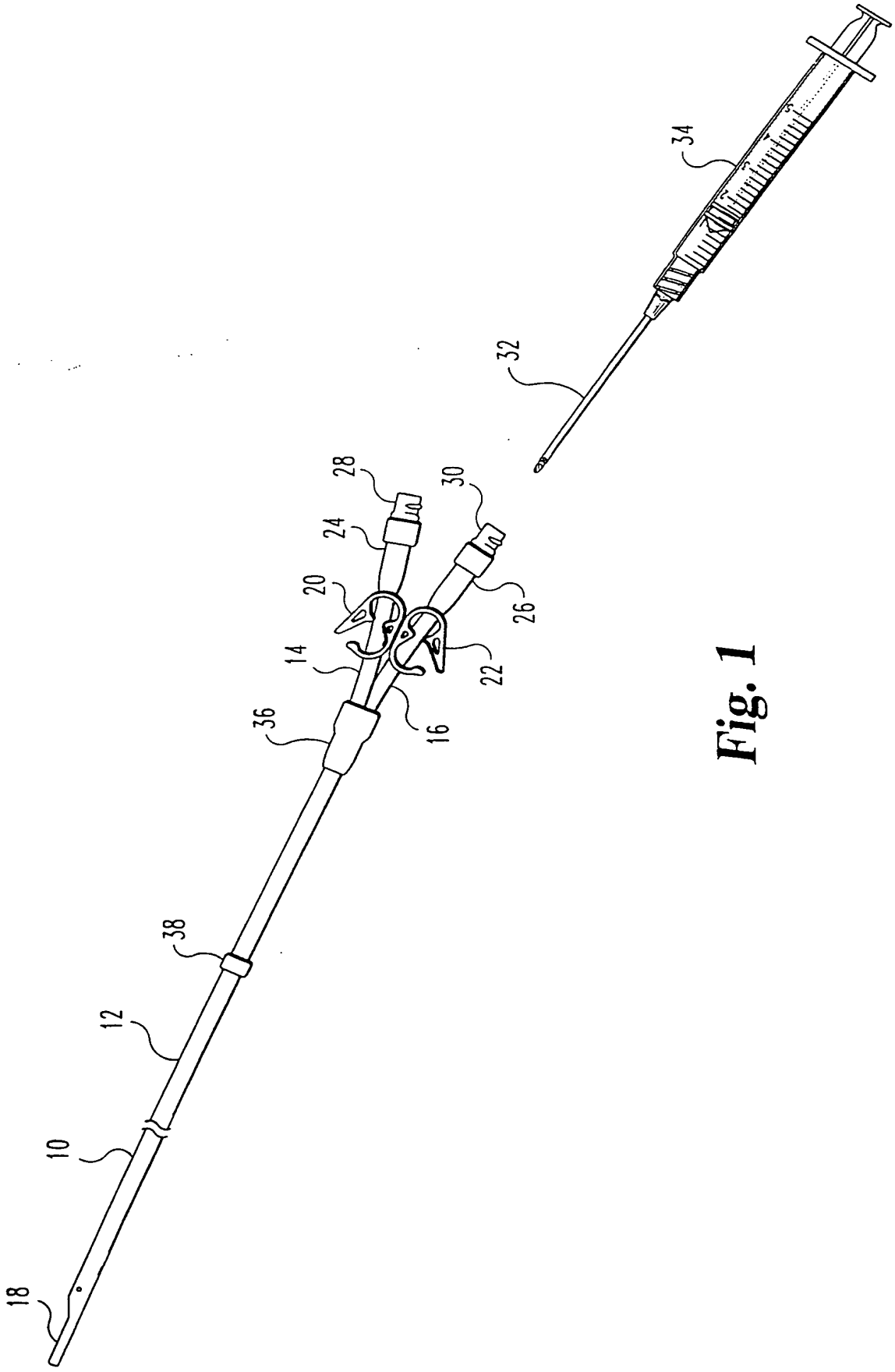


Fig. 1

FIGURE 2

MONTHLY INCIDENCE OF SEPSIS IN ALL PATIENTS, RTC UNIT.

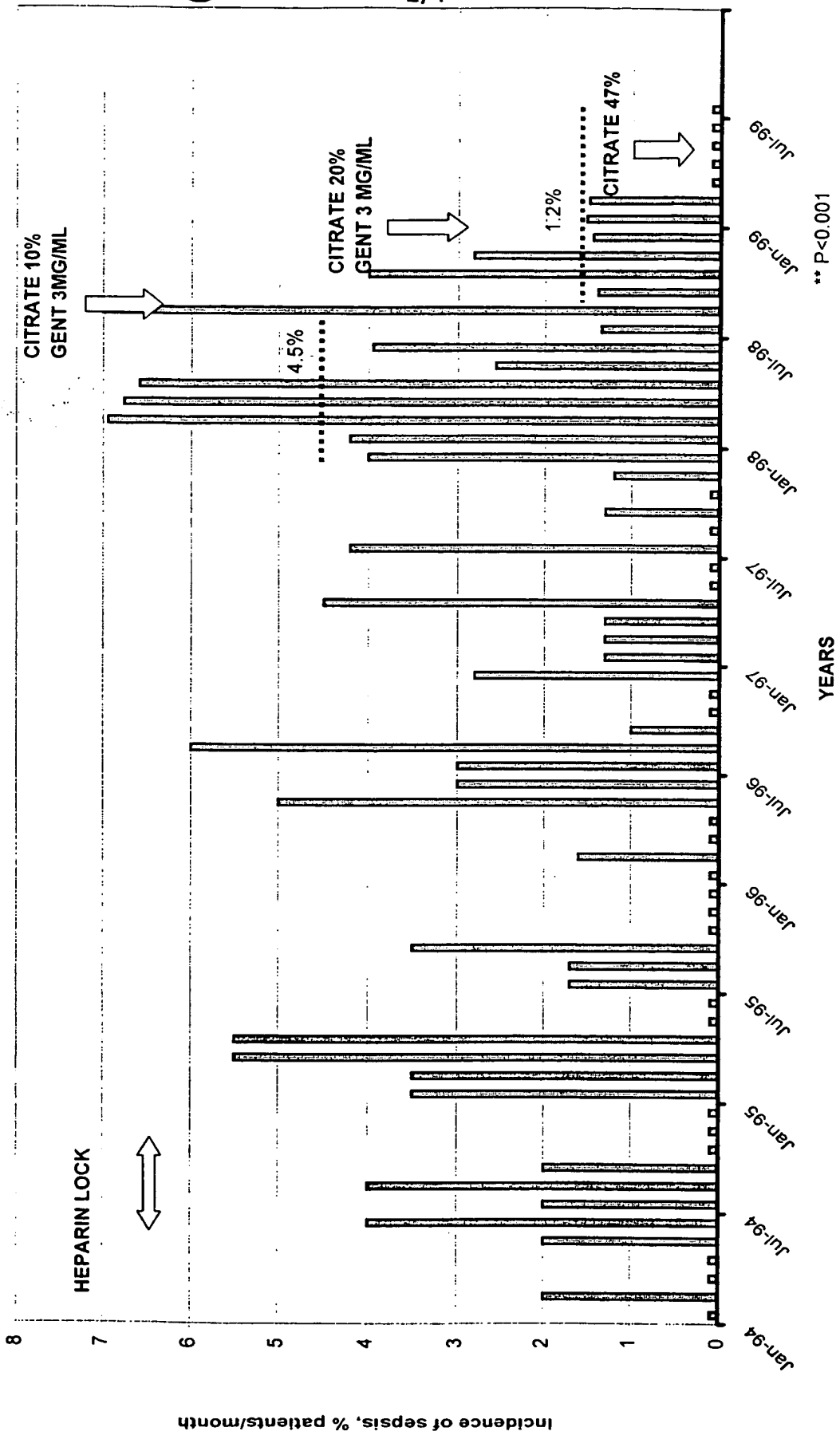
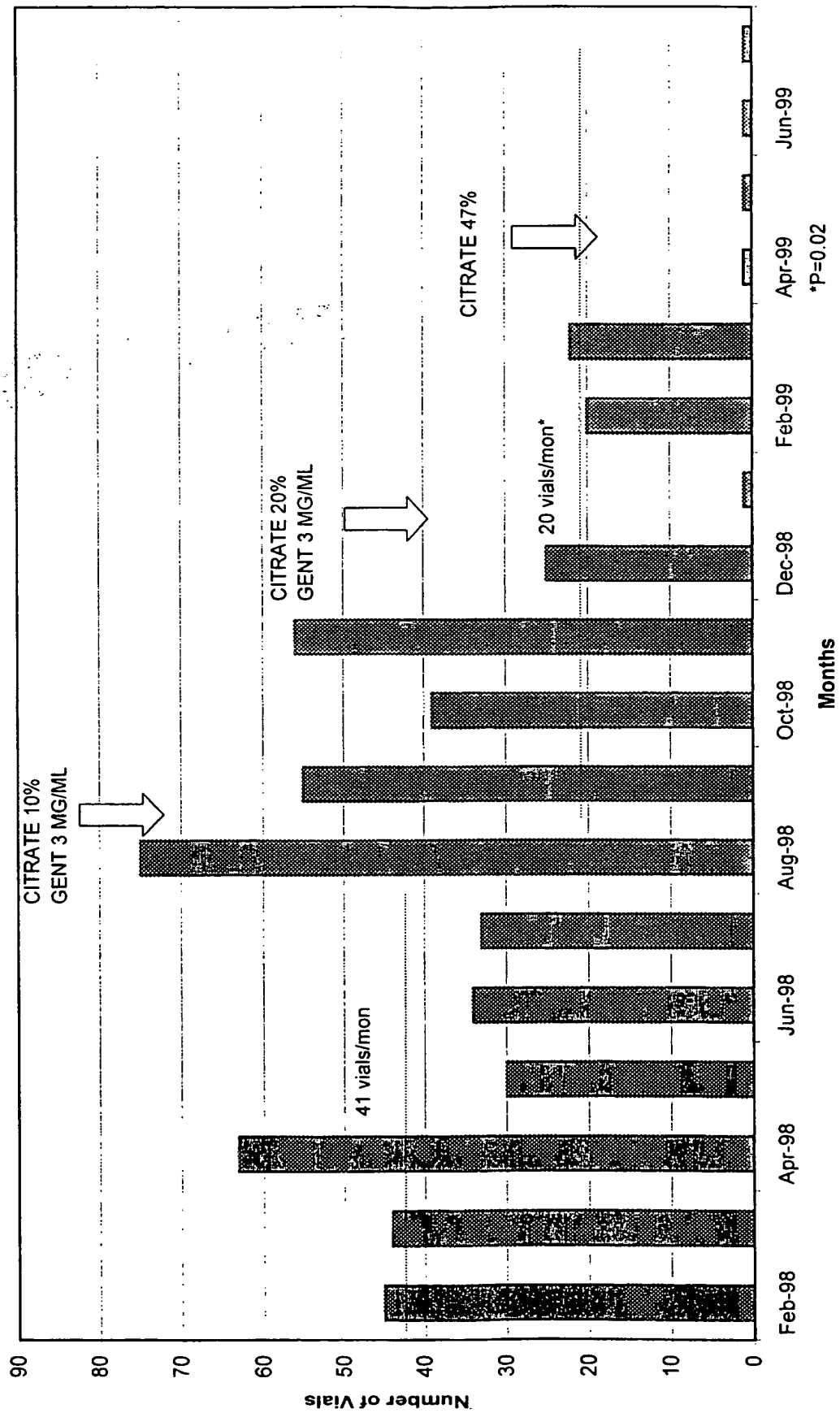


Figure 3
Vials of Urokinase Used For Catheter Occlusion



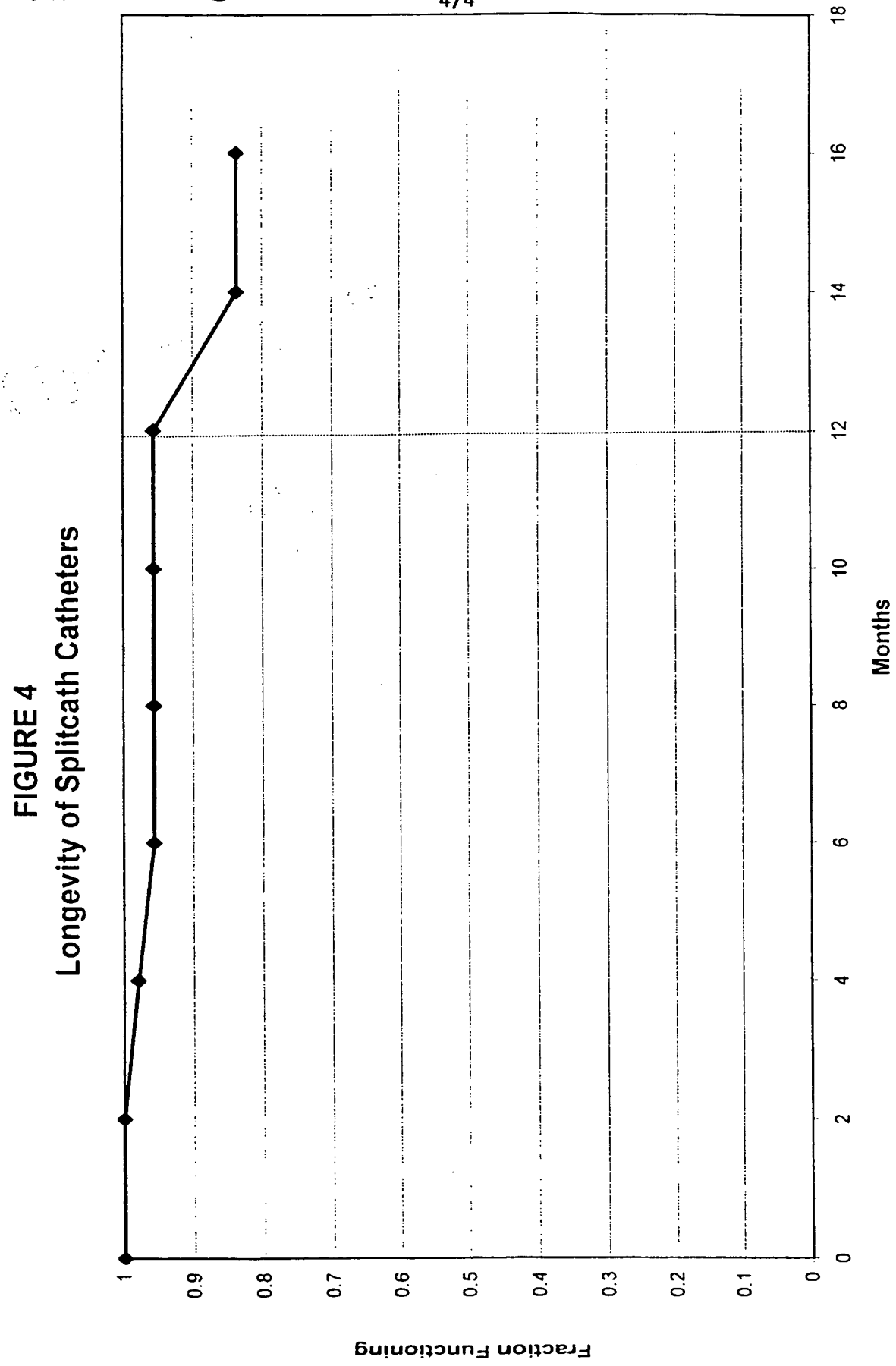


FIGURE 4
Longevity of Splitcath Catheters